MASTERS THESIS

TUBERCULOSIS AND HIV INFECTION IN SOUTHERN ETHIOPIA

BY:
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MAY, 1994 G.C.

TUBERCULOSIS AND HIV INFECTION IN SOUTHERN ETHIOPIA

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AFEWORK GELLETE, MD
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DEDICATION

This thesis is dedicated to my father, Gellete Balcha, and my mother, Tejitu Baruda, for leading their children into intellectual pursuits.

ADDIS ABABA UNIVERSITY

School of Graduate Studies

Tuberculosis And HIV Infection In Southern Ethiopia

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LIST OF ABBREVIATION

AAU	- Addis Ababa University
AFB	- Acid Fast Bacilli
AIDS	- Acquired Immunodeficiency Syndrome
BCG	- Bacillus Calmette Guaerrin
ELISA	- Enzyme Linked Immuno Sorbent Assay
EP	- Extrapulmonary
HIV	- Human Immunodeficiency Virus
IDRC-C	- International Development Research Centre Canada
MOH	- Ministry of Health
PPD	- Purified Protein Derivative
STD	- Sexually Transmitted Disease
TB	- Tuberculosis
WHO	- World Health Organization

ABSTRACT

A health institution based cross-sectional study was carried out in Shashemene town, Southern Ethiopia between September, 1993, and January, 1994, to determine the sero-prevalence and the clinical impact of HIV among newly diagnosed tuberculosis patients.

The HIV-antibody was determined using the two ELISA procedures (Wellcozyme, Wellcome Diagnostics, Dartford Kent England, and Du-pont assay, Singapore).

A total of 450 tuberculosis patients aged 15 years and above were enrolled in the study. The overall HIV-seroprevalence rate was 44.4%. The highest rate was observed in the age group 20-39 years.

A slightly higher HIV-infection rate was found in males (46%) than in females (41%). Those divorced and widowed patients had higher proportion of HIV sero-positivity. The HIV positivity rate was higher for extra-pulmonary than pulmonary form of tuberculosis (OR = 3.80; 95% CI: 1.49, 9.7). Higher proportion of sputum positive patients were HIV-positive compared to the sputum negative pulmonary tuberculosis patients (OR=1.09; 95% CI: 0.64,1.85) though they manifested typical radiographic features (OR = 7.87; 95% CI: 4.39, 14.21).

Significant differences were noted among HIV positives than HIV negatives in manifesting herpes zoster, lymphadenopathy, oral candidiasis, peripheral paraesthesia and chronic diarrhoea.

An alternative diagnostic approach is required to avoid missing HIV-related tuberculosis which is communicable to the general population. Other findings are discussed and recommendations made.

1. INTRODUCTION

Tuberculosis, long known to be a major cause of morbidity and mortality throughout the world, has for the past several decades been a neglected disease in developing countries. However, it is now attracting renewed interest, and significant efforts to revive control activities are currently under way. This is occurring largely because of the increased incidence of tuberculosis in many HIV-endemic countries, the availability of proven effectiveness of short-course chemotherapy, and the realization that TB control is one of the most cost effective health interventions in the developing countries.(1)

An alarming epidemic is sweeping across the developing world- a partnership between TB and HIV, the virus which causes AIDS. With the growing HIV/AIDS problem, the serious TB burden in subsaharan Africa may become even more enormous and may critically overload the already stressed health care system (2).

Tuberculosis remains a health problem of enormous dimensions, particularly in the developing world, affecting millions of people each year. The pandemic of the acquired immunodeficiency syndrome (AIDS) and the evidence of an association between TB and HIV, which causes AIDS is now a further cause for world-wide concern.(3)

Since containment of tuberculosis infection in an individual depends on intact cellular immunity, HIV, due to its ability to destroy the immune system, has now emerged as the most significant risk factor for progression of dormant TB infection to the clinical disease.

As a result, the tuberculosis problem not only has begun to worsen but also poses an unprecedented medical, social and economic threat globally, especially to the developing countries (4).

The overlap between tuberculosis and HIV has ominous social and medical implications particularly for the resource-poor countries. With further increases in tuberculosis cases, considerable pressure has been put on the already fragile and overstretched health services with more demand for diagnostic services, anti-TB drugs, hospital beds, and other supplies and services. In the absence of rapid and effective interventions, increasing numbers of AIDS and TB cases and deaths are likely to occur among adults in their economically most productive years. This may have tremendous social and economic implications.

Since the co-occurrence of tuberculosis and HIV infection has meant that new approaches to TB control are necessary, obtaining baseline data indicating the impact of HIV on tuberculosis deserves priority.

Tuberculosis is rampant in Ethiopia and HIV infection is spreading at an alarming rate. Hence, an examination of the possible influence of HIV infection on the epidemiology of TB in Ethiopia is important, in order to monitor constantly the changes in the epidemiological situation of both TB and HIV/AIDS.

The interaction between HIV infection and TB poses a serious health problem which will result in a major increase in disease, death and health care needs. In areas with high prevalence of infection with both HIV and TB, the incidence of TB appears to be rising (2,3).

Because persons with both infections have an increased risk of developing clinical TB, and further transmitting mycobacterium TB infection, Ethiopia is facing or soon face, a rapid upsurge of the TB problem. Therefore sero-prevalence studies are vitally important to obtain estimates of the level of HIV- infection among TB patients, and to follow trends of infection overtime. Accordingly, this study estimated the magnitude of HIV infection among suspected and/or confirmed TB patients over 15 years of age. The study also examined the clinical presentations among HIV positive and negative TB patients and looked into the impact of HIV on the TB control strategies. Ultimately this sero-prevalence study is undertaken to assess the potential impact of HIV infection on the epidemiology of TB.

2. LITERATURE REVIEW

2.1 The Global HIV/TB situation

WHO has estimated that about 1700 million people, i.e, one third of the total human population, are infected with mycobacterium tuberculosis; more than 8 million new cases of active disease occurred in 1990; and in the same year, nearly 2.9 million deaths were caused by tuberculosis, 90% of them in the developing countries (5). On the other hand, in January 1992 WHO estimated that 9-11 million adults and about one million children, mostly in the developing countries, had been infected with the human immunodeficiency virus (HIV) world wide. Further, more than 1.5 million adult and over half a million paediatric cases of acquired immunodeficiency syndrome (AIDS) may have occurred since the beginning of the pandemic (6).

Considering that the great majority of HIV infections occur in 15-49 year-old,(5,6) and assuming that the risks of infection with HIV and tuberculosis are independent, it has been estimated that world wide more than 4 million persons,again mostly in the developing countries, have been infected with both HIV and Mycobacterium tuberculosis .

The most important risk factor yet identified for the development of tuberculosis following infection is human immunodeficiency virus infection. Very high incidence rates of TB in dually infected individuals have been reported in both industrialized and developing countries (7).

In the developing countries, the overlap between HIV infection and tuberculosis is shown by the high HIV sero prevalence among patients presenting with active tuberculosis. Data from a number of African countries and Haiti show that sero-prevalence ranges between 17% and 66% (2, 8-13).

Globally, the effects of the AIDS pandemic on the TB situation will probably be very serious, adding some 1.5 million new cases of tuberculosis annually. The main factor determining the scale of aggravation of tuberculosis is the age structure of the population infected, or at risk of being infected, with tubercle bacilli and HIV (14).

The impact of HIV infection on the tuberculosis situation is most serious when the prevalence of tuberculosis infection in young adults, who are also at risk of HIV infection, is high. Using estimates of the prevalence of tuberculosis infection in various regions,

it was estimated that in early 1992 there were more than 4 million persons with dual HIV and TB infection world wide; a great majority (3.2 million) of whom live in sub-saharan Africa (15).

Developing countries are faced with the problem of the increased cost of tuberculosis treatment service brought about solely by the increase in numbers of cases. In addition, evidence is accumulating suggesting that cases of HIV associated TB may be more expensive to treat than TB without HIV infection, owing to increased rates of adverse reactions to treatment, recurrent episodes of TB, and HIV related intercurrent infection.

The failure of some measure of resource utilization is difficult to measure, but number of admissions, probably represents the ability of medical workers to limit increases in work load. Also numbers of diagnostic tests for TB have probably increased at a rate proportional to the increase in cases. Utilization of investigation, therapies and other services is more related to HIV status and is likely to have increased out of proportion simply due to the rise in TB cases (16).

2.2 Co- existence of HIV/TB

Mycobacterium tuberculosis is an important pathogen associated with human immunodeficiency virus (HIV) infection and its resulting immunosuppression.

It has been estimated that persons with the acquired immunodeficiency syndrome (AIDS) have more than a 100 fold risk of developing TB compared to the general population (17). HIV- infection results in an impairment of the immune system and entails a substantial risk of further contracting TB in those individuals who are or become infected with the tubercle bacillus. The association between HIV and TB was first recognized in Haitians and intravenous drug abusers (18). Based on available information, it is difficult to reach any conclusion on the relative infectiousness of HIV-associated TB. However there is a fear that the increasing numbers of HIV-positive patients with TB will lead to increases in the transmission of TB in the rest of the population and, thereby, increase the size of the population infected with tubercle in the future.

Although the transmissability may depend on the stage of HIV-infection, it is possible that the rises in the number of TB cases in many countries will increase TB transmission both to the HIV-positive and HIV-negative populations (19).

Tuberculosis is the single most important opportunistic disease in HIV positive individuals and presents a great challenge to clinical and preventive medicine (20).

The HIV pandemic will worsen the TB situation in developing countries in three ways over and above the existing situation (21).

a. By reactivation of a latent TB infection among dually infected persons ;

b. By new infection with tubercle bacilli and rapid progression to active disease in HIV infected persons; and

c. By increasing the number of cases in the general population whose infection and disease is the result of transmission from HIV positive individuals developing TB by either reactivation or recent infection.

The impact of HIV-infection on the epidemiological situation of tuberculosis depends on several factors; in particular, on:(21)

- The prevalence of HIV infection in the community and its trend
- The prevalence of tuberculosis infection in the general population aged 15-49 years.
- The rate of development from tuberculosis infection to active tuberculosis
- The level of and the trend in the annual average risk of tuberculous infection.
- The detection rate of new and relapse cases of TB and the cure rate of smear positive cases.

In comparison with other types of infections associated with HIV-infection, TB appears to develop at a somewhat earlier stage in the progression from HIV-infection to AIDS (22).

2.3 CLINICAL OVERVIEW -HIV/TB

The influence of HIV-infection on the clinical picture of tuberculosis appears to relate to the extent of immunodeficiency due to the HIV-infection. In patients who are markedly immunocompromised, haematogenous dissemination or progressive primary TB appears to be more common. Moreover, pulmonary cavities are uncommon and granulomas in lung tissue are poorly developed (23). The increased TB incidence is mainly due to the depression of cellular immunity caused by HIV infection in subjects previously infected with tubercle bacilli, and only to an extent due to recent infections in previously uninfected subjects, or re-infections in those previously infected. However, if the current risk of TB infection is high and the annual decrease in the risk of infections is low, an excess of infectious TB cases caused by HIV may gradually increase the risk of TB infection in the general population. In conclusion, the current level of the risk of TB and its trend are the most decisive factors in containing the deterioration

of the epidemiological situation of tuberculosis caused by HIV- infection in the future (24).

It is unclear whether HIV- associated TB is usually, the primary, reactivated type, or secondary exogenous infection but what ever the source, people infected by both HIV and mycobacterium TB have an accelerated progression to overt TB. Patients with both HIV infection and TB can present in various ways but while many have the typical clinical and radiographic features of TB, most studies in Africa have noticed a change in the pattern of the disease. Most patients seem to produce no sputum, or have negative sputum smear; chest radiography may show little change, or there may be diffuse pulmonary infiltrates without cavitation. Extrapulmonary disease also appears to be more common. This change in disease pattern has made diagnosis of TB more difficult (24).

The common denominator of AIDS is a profound immuno-suppression, predominantly of cell-mediated immunity, that leads to a variety of opportunistic diseases, particularly certain infections. The main cause of the immune defect in AIDS is a qualitative and quantitative deficiency in the subset of T-lymphocytes termed the T_4 population (25).

There are two distinct but overlapping clinical patterns of tuberculosis in HIV sero-positive persons depending on when the TB develops in relation to HIV-induced immunosuppression (22). At the early stage of HIV-infection, the clinical presentation of TB is much more classical.

Colebunders et al (2) in Kinshasa found classical TB in HIV seropositive patients, who mainly appeared to be at an early stage of HIV infection.

In immunocompetent individuals approximately 5-15% of those infected with Mycobacterium tuberculosis will develop active TB within their life time. Of those, roughly one-third will develop TB within one year of initial infection (26). At least 30% of persons with previous TB infection were capable of undergoing reactivation following HIV infection (29).

The main strategy of TB control is to improve the cure rate by early diagnosis and treatment of tuberculosis cases with primary focus on open (smear positive) cases (28). Thus, besides decreasing individual suffering, effective TB control programmes can limit the increase in transmission of infection, despite a large increase in TB incidence. The principle of this strategy still holds in the face of the HIV pandemic.

Short course chemotherapy is as effective among HIV-negative patients in terms of cure rate as in HIV positives (29).

A high index of suspicion and an aggressive diagnostic approach is required to avoid missing HIV-related tuberculosis which is communicable to the general population and is readily treatable (30). In view of the high risk of tuberculosis in dually infected persons, prevention of TB in such persons is clearly a high priority. Administration of preventive chemotherapy to HIV/TB co-infected persons has therefore been considered as one of the most critical interventions to limit the increase in clinical TB that is expected from the growing pool of HIV/TB patients (31).

During the HIV era TB services in most sub-saharan African countries are already severely strained as health workers try to cope with the emerging problems posed by the interaction of HIV and mycobacterium TB. These include difficulties in diagnosis because of the increased numbers of smear- negative pulmonary disease, increased congestion in those countries who administer the initial intensive phase of treatment in hospital, increased cutaneous hypersensitivity reactions from thiacetazone, increased HIV- related illness during treatment, increased mortality rates and increased relapse rates after completing anti TB therapy (32).

2.4 Ethiopian HIV/TB situation

The first Ethiopian sera found positive for human immunodeficiency virus (HIV) were collected in 1984 (33) and the first seven cases of acquired immunodeficiency syndrome (AIDS) were recognized in 1986 and 1987 (34). A study conducted in 1990, revealed a 30% prevalence of pulmonary and extrapulmonary tuberculosis among one hundred HIV-positive patients analyzed in Addis-Ababa teaching hospital (35).

As in much of the developing world, tuberculosis has been and continues to be a major public health problem in Ethiopia. It is a major cause of morbidity and mortality both in and out of hospitals. Reports from the last five years show that annually about 75,000 to 95,000 patients visit health institutions because of tuberculosis.

TB is also shown among the leading causes of hospital admissions and deaths. Estimates indicate that the number of new infectious cases occurring every year is in the range of 41,000 to 70,000.

The most reliable way to determine the prevalence of tuberculosis infection in Ethiopia is by tuberculin testing with PPD of the non-BCG vaccinated population (36). From 1953 to 1955 the MOH,WHO, and UNICEF tested 609,321 people, finding a net positive rate of 35.9%. This relatively low rate was largely attributed to the large number of children in the survey.

The tuberculin survey of 1990 had revealed a 55 smear-positive pulmonary TB cases/100,000 population. If the overall rate of 1.4% applied to all age groups, it would correspond to 38,500 new contagious cases annually.

Tuberculin surveys, have shown that the risk of infection in rural children is 1.4% annually, while in Addis Ababa it is over 50% higher. In the present HIV era, the problem is expected to worsen. Both HIV and TB strike the most productive ages of the population with a tremendous effect on the socio-economy of a country (36). According to the latest national report the annual risk of infection of TB is estimated to be around 1.5 %. All the same the WHO estimate of the annual risk of infection in sub-saharan Africa ranges between 1.0% to 2.5% while Styblo et al place it in the range of 1.5 to 2.5% (37).

HIV-seroprevalence rates of greater than 40% are common among patients with tuberculosis in many African countries.

In Uganda, 66% of newly diagnosed TB patients were HIV positive; in Zambia 60% of TB patients were HIV infected and in Kenya 30% of newly diagnosed TB patients were HIV positive (38). In Ethiopia one study has been conducted among 106 soldiers in 1988 and revealed a 6.6% seropositivity among TB patients (39).

3. OBJECTIVES OF THE STUDY

General Objective

To assess the magnitude of HIV infection and the relationship between tuberculosis and HIV in TB patients in Southern Ethiopia.

Specific Objectives

1. To measure the sero-prevalence of HIV among TB patients in Shashemene.
2. To describe the clinical manifestation of TB in HIV positive and HIV negative tuberculous patients.

4. SUBJECTS AND METHODS

This health institution based cross-sectional study, was conducted in Shashemene,a town located in Southern Ethiopia, between September, 1993 and January, 1994.

4.1 Study Area and Population:

This study was conducted in Shashemene, a town found 250 kms along the main road from Addis-Ababa to Moyale-Kenya. It has a wide communication network connecting more than four regions of the country.

The source of the study subjects include both inpatient and outpatient departments of Shashemene General Hospital,and Health Centre, and another two health institutions.(Gambo Catholic Hospital and Awassa Health Centre) who frequently refer patients to the Shashemene Hospital for the anti-TB treatment. All new tuberculosis patients who came seeking the services of the health institutions were included into this study. New patients with a suspected or/and confirmed diagnosis of tuberculosis between September 5, 1993 G.C and January 10, 1994 G.C at the local hospital and health centre were entered into the study.

4.2 Enrolment Procedure

The purpose of the study was explained to the heads of health institutions in the study area and then to the clinicians who work there. Physicians in the health centre and hospital were asked to refer all suspected TB cases to the research team for further investigation of the patient. Accordingly a total of four hundred fifty newly diagnosed TB patients were enrolled in the study.

To maximize efficient utilization of the ELISA reagent, patients sera were stored at 20°C in Shashemene General Hospital and later analyzed according to the Kit manufacturer's instructions.

4.3 Sample size estimation:

Using the formula:

$$N = \frac{Z^2(P)(1-P)}{L^2}$$

Z= The critical value corresponding to a 95% confidence level.

L= The degree of certainty for the result to be within this discrepancy.

p= Estimated prevalence.

Where Z = 1.96

P = 0.25

L = 0.04

The desired width of confidence limit of 0.04, an estimated (prevalence) of the sample percentage of 0.25 (based on previous studies) and the confidence level of 95% was taken. This gave a sample size of 450.

4.4 Operational Definitions:

Confirmed TB diagnosis: Pulmonary TB was diagnosed when there are two Acid Fast Bacili(AFB) positive results of sputum specimen; or a patient with one sputum specimen positive for AFB and radiologic abnormalities consistent with active pulmonary tuberculosis.

Suspect case: patient in whom presumptive diagnosis is made on the basis of radiological or other clinical evidence and with negative AFB smear.

New case: Patient who was for the first time diagnosed with tuberculosis.

Disseminated TB: If there are more than two organs, other than pleural and lymph node, affected by the lesion.

HIV-Positivity: patient who turned out to be positive by the combination of Wellcozyme and Dupont assays.

4.5 Data collection and Measurement:

A standardized questionnaire was used to collect demographic and clinical information. Physician, from each health institution filled out the questionnaires.The questionnaire was checked for consistency and clarity upon collection by the principal investigator regularly.

Incomplete and misfilled questionnaires were sent back to the responsible physician for correction on the same day.

In this questionnaire, information relating to their history and clinical examination was completed for each patient, radiological and laboratory results were recorded and blood samples taken by laboratory technicians. Diagnosis of tuberculosis was made using the various combinations of clinical information, radiographic findings, laboratory results and response to therapy (presumptive).

All patients with pulmonary tuberculosis had a chest X-ray. Radiological features, including the zones involved and the presence or absence of cavities, were recorded by the physician at the time of recruitment.

Seroprevalence was determined for all new TB patients who were 15 years of age and above, irrespective of the lesion site. All patients with suspected/ confirmed TB were enrolled for the analysis of clinical presentations. Patients seen at the health institutions were treated according to the national guidelines by the respective health units. Serum samples were analyzed for the HIV antibody by a competitive recombinant enzyme linked immunosorbent assay (Wellcozyme, Welcome Diagnostics, Dartford, Kent UK) and antiglobulin recombinant ELISA assay(Dupont, Singapore). There are as yet, no reports of HIV-2 in Ethiopia.

Throughout this text HIV-1 seropositivity is referred to as HIV-seropositivity.

Procedures were performed according to the kit manufacturer's instructions. Only those sero-positive on both assays were considered HIV-positive. Studies in Addis Ababa (40), Kenya (41), and Zambia (2,42) showed this definition to be concordant with Western-Blot for HIV-1. This examination strategy is also supported by a recent WHO report (45). Sputum was examined for acid fast bacilli on direct smear using Ziehl-Neelsen stain and fluorescence microscopy with a 25 x objective and 6.5 x eye pieces. Serological testing were carried out anonymously, with all clinical and laboratory data being identified only by a code number.

A chest X-ray was performed for all pulmonary tuberculosis patients and read by three general practitioners (with similar year of experience) who have undertaken special training on the radiology of the chest to run the tuberculosis follow-up clinics.

4.6 Variables measured

Socio-demographic characteristics: age, sex, marital status and occupation.

Clinical data: Major symptoms and signs of TB and HIV infections were reviewed. History of STD and hospitalization due to TB were obtained and HIV status of each patient determined.

4.7 Data Processing And Analysis

Data entry and analysis were done using EPI INFO (43) and SAS (44) computer statistical packages. Initial analysis of the association between HIV seropositivity and various variables were performed using standard 2 x 2 tables. Further analysis were carried out using logistic regression. Where appropriate, Maentel Haenszel Chi-square methods were applied to test for trends. The odds ratios (OR) presented are the antilogs of the logistic regression co-efficient. Ninety-five percent confidence intervals were calculated and statistical significance was designated at $P < 0.05$.

4.8 Ethical Consideration;

Patients were informed of the study procedures and the tests to be made during the investigation. Informed verbal consent was obtained from each participant.

Every precaution was taken to respect the privacy of the patient and anonymity was assured by the use of code numbers during specimen processing. TB treatment was free for all study participants and anti-TB drug stock adequate for full course was secured for both study centres.

Refusal of a patient to participate in the study has not interfered with the routine doctor-patient relationship. Those who refused to participate followed the routine procedure in the health units.

Counselling service to be offered to HIV positive patients was organized in collaboration with the Zonal Health Department prior to the initiation of the study. The study was approved by the ethical committee of both the Department of Community Health and Faculty of Medicine, Addis Ababa University.

5. RESULTS

Between September, 1993 and January 1994, a total of four hundred fifty tuberculosis patients were enrolled in the study.

Of the 450 patients there were 269 (60%) males and 181 (40%) females. The mean age of the patients was 30 years. Most patients 254 (56%) were from Shashemene, 97 (22%) were students, farmers and housewives accounted for 17% each. The remaining 203 (45%) belonged to different other occupations. (Table 1).

Overall, 199 (44%) of the patients were positive for HIV. There were nine indeterminate results who were negative by Wellcozyme and positive by the Du-pont assay. These patients were considered as HIV negatives.

Demographic factors and HIV status:

As indicated in Table 1, there was no statistical difference in HIV sero-prevalence with regard to age and sex. However, in the age group 20-39 and in male patients HIV positivity was found to be higher. The peak sero-prevalence occurred in the age group 20-29 years. There was no trend of positivity observed with age increment (p- trend= 0.22).

Table 1. Relationship between HIV Positivity Demographic and potential Risk Factors Among Tuberculosis patients. Shashemene, 1994.

	HIV Status		
	Positive No (%)	Negative No (%)	OR (95% CI)
Age			
15-19	27 (40.9)	39 (59.1)	1*
20-29	76 (47.8)	83 (52.2)	1.48 (0.86, 2.56)
30-39	62 (46.6)	71 (53.4)	1.56 (0.92, 2.64)
≥ 40	34 (36.9)	58 (63.1)	1.18 (0.61, 2.25)
Sex			
Male	124 (46.1)	145 (53.9)	0.84 (0.57,1.2)
Female	75 (41.4)	106 (58.6)	
Marital Status			
Single	100 (50)	103 (41)	1*
Married	79 (40)	135 (54)	0.60 (0.40, 0.88)
Other	20 (10)	13 (5)	1.56 (0.73, 3.3)
History of STD			
Yes	125 (63)	145 (58)	1.23 (0.83,1.84)
No	74 (37)	106 (42)	
Occupation			
Farmer	25 (33)	50 (67)	1*
Student	32 (33)	65 (67)	0.98 (0.51, 1.86)
Driver	9(35)	17 (65)	1.05 (0.40, 2.7)
House-wife	27 (36)	48 (64)	1.12 (0.57, 2.2)
Daily labourer	13 (52)	12 (48)	2.15 (0.85, 5.4)
Ex-Soldier	26 (55)	21 (45)	2.46 (1.16, 5.2)
Merchant	22 (59)	15 (41)	2.91 (1.28, 6.59)
Prostitute	9 (60)	6 (40)	2.97 (1.94, 3.4)
Gov't employee	23 (64)	13 (36)	3.50 (1.50, 8.1)
Other	13 (76)	4 (24)	6.5 (1.92, 22.1)

* Reference category

Overall 124 (46%) of the males were sero-positive compared with 75 (41%) of the females, but statistical significance was not noted after allowing for age (OR = 0.84; 95% CI: 0.57, 1.21).

The marital status of patients was divided into three categories, those who were single, married and other (divorced, widowed, separate). There was a statistically significant association between marital status and HIV positivity.(OR=0.60, 95% CI :0.40,0.88 $p<0.05$).The association persisted even after adjusting for age and sex. Patients who were widowed/separated or divorced had higher prevalence of HIV positivity. Occupational categories which most contributed to HIV positivity in descending order include government employees, prostitutes, merchants,

ex-soldiers, and daily labourers.(Table 1).

Although no significant association was observed in this study between HIV positivity and other sexually transmitted diseases, most patients (60%) reported to have one or more history of sexually transmitted disease (other than HIV), in the past.

Table 2, shows the prevalence of the HIV antibody according to the type of tuberculosis. A much higher prevalence of HIV antibody was found among those with pleural, lymphnode and disseminated tuberculosis than among those with pulmonary disease.

The difference in HIV status was independent of age and sex. The finding is statistically significant at $p<0.05$. The adjusted OR is 3.80; 95% CI: 1.49-9.97, $P<0.05$) which is similar to the crude estimate.

Two hundred sixty nine patients were diagnosed to have pulmonary disease on the basis of clinical findings, radiographic and/or sputum smear results. In 128 (48%) of them tubercle bacilli were identified by the Ziehl Neelson stain method. In this study, patients with extrapulmonary tuberculosis were more likely to be HIV sero-positive than were patients with pulmonary lesions.

Table 2, shows the relationship between HIV status and site of tuberculosis. Extrapulmonary disease (pleural, lymphnode, disseminated) both alone and in combination with parenchymal lung disease, was strongly associated with HIV infection (OR = 3.92; 95% CI: 1.54, 9.9) $P < 0.05$. The association persisted when adjusted for age and sex (OR = 3.80 95% CI: 1.49, 9.7) $P < 0.05$. The lungs were, however, the commonest site of the disease in both HIV positive and negative patients.

Table 2. Association between Sites of Tuberculosis and HIV Seropositivity. Shashemene, 1994.

	HIV Status		OR (95% CI)	
	Positive n=199	Negative n=251	crude	Adjusted**
Pulmonary	95	174	1*	1*
Pleural	12	6	3.66(1.33,10.0)	3.45(1.24,9.55)
Disseminated	28	27	1.89 (1.05,3.40)	2.02(1.11,3.65)
Lymphnode	49	37	2.42 (1.47,3.97)	2.48(1.50,4.11)
Pulm + EP	15	7	3.92(1.54, 9.9)	3.80(1.49, 9.7)

* Reference category

** Adjusted for age and sex by logistic regression.

The overall proportion of hospitalized tuberculosis patients was 29%. Out of these only 41% were positive for HIV infection, while 46% of the ambulatory TB patients were sero-positive. The sero-prevalence of HIV infection in hospitalized TB patients was not significantly different from those who attended the out-patient department. No significant association between HIV status and sputum examination result for AFB was observed in this study.

Table 3. Radiographic Findings in Cases with Pulmonary Tuberculosis in relation to HIV Infection. Shashemene, 1994

X-ray findings	HIV Positive No (%) n = 95	HIV Negative No (%) n = 174	OR (95% CI)
Upper zones only			
Yes	70(48)	76(52)	
No	25(20)	98(80)	3.61 (2.02,6.48)
Middle/Lower Zone			
Included	35(30)	80(70)	
Not Included	60(39)	94(61)	0.69 (.40,1.18)
Cavitation			
present	65(45)	79(55)	
Absent	30(24)	95(76)	2.61 (1.49,4.56)

Chest X-rays were available for all pulmonary TB patients. The chest X-rays showed pulmonary cavitation in 79 (55%) of the HIV negative, but in only 65 (45%) of those HIV-positives. (OR = 2.61; 95% CI: 1.49, 4.56, P < 0.05 Table 3). Seventy six (52%) of the 174 HIV negative pulmonary TB patients had predominantly of upper zone lesions compared with 70 (48%) among the 95 HIV positive cases. (OR = 3.61; 95% CI: 2.02, 6.48, P < 0.05). When the association between HIV status and AFB positive sputum smear were stratified for the presence of cavitation and superior segment involvement, trends were still present, but were less marked and were not statistically significant.

As shown in Table 4, nearly equal proportions of patients who had upper lobe infiltration remained to be sputum smear positives and negatives; and most sputum positives appeared to have pulmonary cavitation (OR = 7.87; 95% CI: 4.39, 14.21).

Table 5, shows the relationship between symptoms and signs at presentation and HIV status. A significant number of sero-negative TB patients had complained of cough and fever. Prolonged history of cough and fever was also reported by a large proportion of TB patients.

There was no significant difference in the history of marked weight loss and organomegaly among the HIV positive and negative patients. A large proportion of patients who presented with lymphadenopaty were positive for HIV.

Table 4. Asociation between Sputum Smear Positivity and Selected Radiographic Appearance among Pulmonary TB Patients. Shashemene, 1994.

	Sputum for AFB		
	Positive	Negative	OR (95% CI)
Cavity			
Present	100 (69)	44 (31)	
Absent	28 (22)	97 (78)	7.87 (4.39, 14.21)
Upper zone involvement			
Yes	52 (52)	48 (48)	
No	76 (44)	93 (56)	1.33 (0.78, 2.24)

Clinical signs and symptoms which showed an association with HIV infection were generalized lymphadenopathy, oral candidiasis, herpes zoster, chronic diarrhoea and paraesthesia. Sputum positive tuberculous patients showed a slight difference from sputum negatives in the development of fever. Most sputum negative patients had a more prolonged fever than the others. Large number of sputum negative patients tended to manifest with chronic cough than smear positive patients ($x^2 = 29.15$; df = 2, $P < 0.001$).

Table 5. HIV Sero-positivity and Selected Clinical Findings among Tuberculosis Patients. Shashemene, 1994.

Clinical Findings	HIV +ve n = 199 No (%)	HIV -ve n = 251 NO (%)	OR (95% CI)	P
Candidiasis				
Present	12 (6)	5 (2)	3.16 (1.02, 10.4)	0.02
Absent	187 (94)	246 (98)		
Lymphadenophaty				
Present	58 (29)	51 (20)	1.61 (1.02, 2.55)	0.03
Absent	141 (71)	200 (80)		
Herpes Zoster				
Present	14 (7)	6 (2)	3.46 (1.21, 10.3)	0.008
Absent	185 (93)	245 (98)		
Hepatomegaly				
Present	35 (18)	52 (21)	0.82 (0.49, 1.35)	0.40
Absent	164 (82)	199 (79)		
Splenomegaly				
Present	164 (15)	199 (79)	1.22 (0.74, 2.03)	0.40
Absent	35 (85)	52 (21)		
Paraesthesia				
Present	30 (15)	17 (7)	2.44 (1.25, 4.80)	0.004
Absent	169 (85)	234 (93)		
Marked weight loss				
Present	124 (62)	155 (62)	1.02 (0.69, 1.53)	0.90
Absent	75 (38)	96 (38)		
Fever				
None	8 (4)	10 (4)	1*	
< one month	67 (34)	92 (96)	0.91 (0.34, 2.4)	0.5
≥one month	124 (62)	149 (59)	1.04 (0.39, 27)	
Cough				
None	40 (20)	40 (16)	1.0*	
< one month	35 (18)	42 (17)	0.83 (0.44, 1.56)	0.45
≥ one month	124 (62)	169 (67)	0.73 (0.44, 2.04)	
Diarrhea				
None	153 (77)	221 (88)	1.0*	
< one month	32 (16)	18 (7)	2.56 (1.39,4.74)	0.008
≥ one month	14 (7)	12 (5)	1.68 (0.75, 3.74)	

Reference category

6. DISCUSSION

The sero-prevalence rate of 44.4% in this study is consistent with other studies conducted in Sub-Saharan Africa, the Caribbean and in some urban areas of the United States that have shown a 20-60% of tuberculosis patients to be HIV sero-positive (3,4). However this rate is much higher than that previously reported from Ethiopia in 1990 (39). This marked difference could be attributed to study size differences and to the nature of the rapid dissemination of HIV infection over time, with essential consideration of the time of introduction of the virus in the country and the level of immune compromise. Although evidence on the proportion of HIV/AIDS patients who developed tuberculosis is required; this study partly supports the new HIV/AIDS case definition for Ethiopia which consideres TB as a major criterion.

Though it is essential to note, it was difficult to compute the proportion of TB patients who met the AIDS case definition of this country. The difficulty arised from the presence of various options of the definition itself. The 44% prevalence of HIV infection among tuberculosis patients is higher compared to the other groups in the country who have been screened for HIV, including bloo2d donors (11%) and antenatal clinic attenders (9%).

The most likely explanation for the increased rate in this study is an accelerated progression to tuberculosis among persons who harbour infection with mycobacterium tuberculosis and are also infected with HIV. The findings in this study is in conformity with the other observations that have been noted in the USA, Europe and Africa (2, 5-13, 17).

The seroprevalence rate obtained among the urban-rural community could further be supported by the preliminary findings from another study in this country, that indicated the potential spread of HIV infection from urban to rural areas (46).

The male preponderance (1.5:1) observed for the tuberculosis infection should be regarded as reflection of the pattern of hospital visits in this country, which is 1.2:1 (36). This study also showed more HIV sero-prevalence among males (1.6:1) than females, this observation is in conformity with the national HIV trend that revealed a 1.7:1 ratio (40).

The higher sero-positivity observed in this study among the age group 20-39 is comparable with other African studies (2,7,9,16). The younger ages at which sero-reactive persons developed tuberculosis probably reflects the age prevalence of HIV sero-positive persons in the community as reported from the surveillance data in this country (40).

This evidence reinforces the socio-economic hazard of the co-existence of HIV/TB and indicates the direction of public health activities concerning HIV/TB prvevention and control.

Distribution of HIV positivity across the various professions in this study indicates the trend of sharing equal exposure risk in the community. Accordingly, the practice of concentrating on specific group of the population while addressing health education deserves re-consideration.

The association of HIV infection with marital status is compatible with the known transmission dynamics of HIV. The single being at a higher risk of acquiring the infection. The apparent lack of association between previous history of sexually transmitted diseases and HIV infection doesn't necessarily mean that there is no predisposing role of STDs to HIV/AIDS.

The sero-prevalence of HIV-infection in hospitalized TB patients was not significantly different from those attending the out-patient department. However, inferences regarding the prevalence of HIV infection in hospitalized TB patients depends on many factors that may have changed over time, such as HIV specific mortality rates and criteria for hospital admission and discharge. Examination of this variation between the two sources of TB patients is required through further study.

In this study 29% of the patients with tuberculosis were admitted to the hospital for anti-TB treatment. This is much higher than reports during the pre HIV/AIDS era, which was 15% (36). This clearly shows the profound effect of HIV on work load of hospitals. The impact of HIV on resource utilization like hospital beds, diagnostic investigations and therapies was also implicated elsewhere (16). This also reinforces the importance of educating all personnel involved in health care to take precautions against occupational exposure to HIV with all patients and to avoid possible nosocomial infections. In the absence of rapid and effective interventions, increasing numbers of HIV/TB cases are likely to occur and affect hospital admissions in Ethiopia.

In this study the lung was the commonest site of disease in both HIV positive and negative patients. Only 23% of HIV positive had a positive sputum smear. Even though the absolute number:-46 was much less than the number of sputum positive HIV negative cases, the role of HIV for the spread of the disease in the community should not be underestimated.

The findings in this study re-emphasized the association between HIV and extrapulmonary TB (7). Since pulmonary disease is more important in the field of public health, thus the contribution of HIV positive TB

patients to the spread of the disease is likely to be greater despite this association of HIV with extrapulmonary disease .

The proportion of HIV positive TB patients who had extrapulmonary infection alone (35%) was similar with that reported in a cohort study in Zambia (42), but was higher than other studies done in Zaire, Haiti and Ivorycoast (2,12,13). This discrepancy could have resulted from bias towards pulmonary disease during recruitment in those studies which were conducted at TB referal centres.

As shown in Tables 3 and 4, patients with pleural and lymphnode tuberculosis were more likely to be HIV seropositive than others. Lymphadenopathy remains the most frequent form of extrapulmonary TB as reported from Central Africa Republic, Kenya, Zambia and Brazil (7). Studies from Zaire and Zambia also showed that patients with suspected TB and with extrapulmonary TB had higher HIV seropositivity rates than patients with sputum confirmed TB (2,15). This fact should be seen in light of an essential consideration; i.e., a general shift of trend from pulmonary to extrapulmonary tuberculosis in the present HIV/AIDS era is prevailing, thus leading to diagnostic difficulties by challenging/impeding the available diagnostic possibilities.

Similar with other evidence obtained (2,12,41), there was no remarkable differences in HIV sero-positivty among sputum smear positive and negative pulmonary TB patients. However, this is in conflict with most studies which revealed HIV positive patients to have a negative sputum smear (9). This variation may account for the level of immuno-deficiency posed by HIV infection and prior exposure to TB. In spite of the lack of association, this observation indicates that missing pulmonary tuberculosis patients with HIV could be a distinct possibility. The negative sputum smear among HIV positive patients probably indicates that HIV positive TB patients may frequently have dry cough. The TB detection rate based on sputum smear examination may thus be comparable to that described for HIV sero-negative patients, at least during the early stages of HIV disease (7).

The classic form of TB, with cavitating, upper zone, pulmonary lesions, is known to be determined by the interaction between the bacillus and the host's immune system, so that in the presence of immuno-deficiency a different outcome may be expected (9).

In this study pulmonary cavitation was observed more often in HIV sero-negative TB patients when compared with HIV sero-positive TB patients.

This finding is incompatible with other reports (2,7,), and could be explained by the low grade immuno-depression in the study subjects, leading to the typical cavitary lesion. Similar findings have been reported (17,18) attributing the lesion to the interaction between the bacillus and the host's immune system.

In contrast to other evidence elsewhere (7,17,18) this study revealed that most HIV negative patients with pulmonary tuberculosis tend to have the classic upper lobe involvement. However, a large proportion of HIV positive patients had atypical presentation having supplementary middle/lower zone involvement and non cavitary appearance. These findings further strengthen the distorted radiographic appearance of TB patients which was established elsewhere (7).

A discrepancy between pulmonary cavitation, sputum positivity and upper lobe involvement was observed in this study. All sputum positive cases did not show cavitation and /or upper segment involvement. It has been observed that even in the absence of cavitation the profound impairment of the immunity seen in HIV infection may permit tubercle bacilli to multiply in such large numbers as to become visible on smear examination (12). Therefore the above finding could probably be supported by this fact.

Both tuberculosis and HIV infection lead to chronic ill health and wasting, and both are associated with persistent cough and fever. These characteristics were also seen in this study, illustrating the difficulties in clinical diagnosis. Patients with tuberculosis, with or without HIV infection, might be diagnosed as having HIV/AIDS alone and might therefore fail to receive the anti TB treatment.

This study examined the impact of HIV on the process of diagnosis of TB. Symptoms of TB were comparable in both groups. HIV positive and negative patients, had similar complaints of cough, although fever was more frequent and of longer duration in HIV positives.

The presence of generalized lymphadenopathy, peripheral paraesthesia, herpes zoster, oral candidiasis and diarrhoea may assist in identifying patients with dual infection with tuberculosis and HIV but do not contribute to the diagnosis of TB it self. The lack of association between HIV and prolonged diarrhoea in this study could be attributed to possible recall bias. The tendency of sputum smear negative patients to manifest with prolonged cough and fever further threatens the sputum detection rate , thus compounding the difficulty of clinical diagnosis of pulmonary tuberculosis.

In the absence of a quick and cheap diagnostic test, physicians may be obliged to treat for TB patients with prolonged fever, cough, weight loss, negative sputum smear for acid fast bacilli and failure to respond to standard antibiotics, without confirmation of the diagnosis where HIV and TB are common.

It is worth mentioning that this cross-sectional study lacks information about the role of HIV infection on tuberculosis relapse. A longitudinal design that addresses this factor is to be recommended.

It is to be noted that there are certain limitations to the study.The nature of the study itself has limited the collection of complete information from the patients regarding the clinical signs and symptoms, nevertheless, since all new tuberculosis patients seen at the health institutions during the study period were included in the study, and the physicians involved in clinical examination of patients were the same, it is assumed that in general,the information obtained were comparable for all patients.

Confirmation of TB diagnosis was not possible because of the inherent limitation of the diagnostic tests. Lymph node biopsy could not be done for logistic reasons. But it is believed that the limitations pointed out would not compromise the main findings of the study.

The urban-rural mix of the study subjects and uniformity of the selection criteria used for enroling new TB patients with adequate sample size permits to the internal validity and wider generalizability of the study findings.

7. CONCLUSION

The high prevalence of HIV in patients with tuberculosis suggests that an epidemic of TB is arising in those who are infected with HIV.

Unless the results of HIV tests are known many patients with TB who have no HIV infection might be reported as having AIDS. On the other hand, if tuberculosis is excluded from AIDS reporting then one of the opportunistic infection most often associated with HIV will go unreported as related to HIV. Therefore physicians should develop a high index of suspicions to test for HIV among those risk groups noted in this study.

Because of relatively high HIV sero-prevalence, TB patients could be used as sentinel populations to detect HIV-related illnesses.

This study re-emphasized the severity of the new epidemic of TB and its impact on young adults.

It has also demonstrated difficulties in the clinical diagnosis of co-infected patients who manifested a bizarre clinical, laboratory and radiographic features. An aggressive diagnostic approach is required to avoid missing HIV - related tuberculosis which is communicable to the general population.

The urban rural mix of the study subjects also high lights the spread of HIV infection to rural Ethiopia, implying the need of sharing intensive health education with the urban community.

Sputum smear detection should not be considered as the only reliable indicator for the diagnosis of pulmonary tuberculosis.

The inevitable TB explosion in Ethiopia would affect the load of health institutions, in terms of utilization of diagnostic, therapeutic, and hospital admissions. Hence, the direction of resource allocation for implementing an efficient TB control programme deserves a high priority.

8. RECOMMENDATION

From the results of this study the following recommendations are made.

1. This study lacks the knowledge concerning the course of HIV infected TB patients following anti-TB treatment. Further work is needed to determine the outcome of TB management.
2. The National TB Control Programme and all concerned, should re-direct resource priorities, to TB control for its efficiency, and consideration of the impact of HIV infection on the tuberculosis would be essential, particularly during the planning process and other management activities.
3. Since the already over-worked TB treatment centres are further stressed by the HIV - infection, respective health service organizations should look for possible expansion of the available centres.
4. The dissemination of HIV to the rural communities calls for the need of addressing health education irrespective of the geographic set-ups.
5. The clinical overlap between HIV/AIDS and tuberculosis raises the need of having a possible integration or link between the National TB and AIDS Programmes, in order to monitor the epidemiologic pattern of dual infections.

6. This study demonstrated the danger that the diagnosis of tuberculosis may be missed or delayed in patients with HIV.

   Therefore suspected cases who fail to respond to broad spectrum antibiotics may be started on a trial of anti- tuberculosis therapy. The National TB control strategies also need to be revised in terms of diagnostic, and therapeutic considerations.

7. Training of personnel in hospitals on nosocomial infections and correct diagnosis of both HIV/AIDS and TB.

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10. APPENDIX A

CLINICAL FORMAT

FOR PATIENTS WITH TUBERCULOSIS

Todays, Date D_____ M _____ Y _____

Form Filled by

_____

1. Name of the patient

_____

2. Address: Region_____ Zone _____ Woreda _____

Higher_____ Kebele_____

_____

3. Age _____

4. Sex 1. Male _____ 2. Female _____

5. Occupation

1. Prostitute 2. Farmer 3. Ex-soldier
4. Daily labour 5. Driver 6. Merchant
7. Student 8. Housewife 9. Gov't Employee
10. Other (specify) _____

6. Marital status

1. Single (never married)
2. Married
3. Divorced 4. Widowed 5. Separated

7. Code number of the blood sample

_____

8. HIV status of the patient (coded)

8.1. First screening 1. Positive 2.Negative

3. Other

(specify)_____

8.2. Confirmation 1. Positive

2. Negative

3. Other

9. Type of the patient

Status	Type

1. New case

1.1 Disseminated 1.2 Pulmonary

1.3 Lymph node TB

2. On Treatment

2.1 Disseminated 2.2 Pulmonary

2.3 Lymph node TB

3. Relapse

3.1 Disseminated 4.2 Pulmonary

3.3 Lymph node TB

4. Defaulter

4.1 Disseminated 4.2 Pulmonary 4.3 Lymph node TB

10. Laboratory Results

10.1 Local laboratory

Date Of Examination _____

Sputum result 1. Positive

2. Negative

3. Other

(specify) _____

10.2 Reference laboratory

Date Of Examination _____

Sputum result 1. Positive

2. Negative

3. Other(specify)

10.3 Biopsy Result indicating lymph node TB

1. Yes 2. No 3. Other

(specify) _____

11. X-ray findings

11.1 Involvement of middle/lower zone only

1. Yes 2. No

3. Other (specify) _____

11.2 Involvement of upper zone

1. Yes 2. No

3. Other (specify) _____

11.3 Cavities present 1. Yes 2. No

CLINICAL NOTES

12. History of Fever

    1. None 2. < one month 3. ≥ one month

13. History of Cough

    1. None 2. < one month 3. ≥ one month

14. History of Diarrhoea

    1. None 2. < one month 3. ≥ one month

15. History of Paraesthesia

    1. Present 2. Absent 3. Other (specify)_____

16. Generalized Lymphadenopathy

    1. Present 2. Absent

    3. Other(specify)_____

17. Oral Candidiasis

    1. Present 2. Absent 3. Other (specify)_____

18. Herpes Zoster

    1. Present 2. Absent 3. Other (specify)_____

19. Splenomegaly

    1. Present 2. Absent

    3. Other(specify)_____

20. Hepatomegaly

1. Present 2. Absent 3. Other

21. History of STDs

1. Yes 2. No 3. Other(specify)

22. Marked weight loss >10% of body weight in 6 months

1. Yes 2. No 3. Other

23. History of hospitalization due to tuberculosis

1. Yes 2. No 3. Other

(specify) --

DECLARATION

I the undersigned, declare that this is my work and that all sources of material used for this thesis have been duly acknowledged.

Name--Dr. Afework Geilete

Sign--------

Place--Addis Ababa

Date of submission--May, 13, 1994

This thesis has been submitted for examination with my approval as University Advisor.

Dr. Derege kebede ----------

Advisor

13 May '94